

**DOCKET NO: ISIS0064-100 (RTS-0175)****PATENT****REMARKS**

Claims 1, 2, 4-10, 12-15 are pending in the application. Claim 1 has been amended herein, support for which can be found at, for example, page 94, lines 3 to 8 of the specification. No new matter has been added. Claims 1, 2, 4-10, 12-15 will remain pending.

**I. The Claims Are Clear And Definite**

Claims 1, 12, 13, and 15 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Office Action, at page 2, alleges, "In claim 1, lines 1 and 3, the metes and bounds of the term 'compound' cannot be determined." Applicants respectfully disagree.

Amended Claim 1 recites:

A compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding human dual specific phosphatase 5 (SEQ ID NO:10), wherein said compound inhibits the expression of human dual specific phosphatase 5 by at least 40%.

The metes and bounds of the term "compound" are definite and encompass a compound that is 8 to 50 nucleobases in length. Additionally, the compound is targeted to a nucleic acid molecule encoding human dual specific phosphatase 5 (SEQ ID NO:10), and the compound inhibits the expression of human dual specific phosphatase 5 by at least 40%. Further, the term "compound" is a term of art that is quite well recognized by those skilled in the art and can be found in numerous dictionaries should one skilled in the art desire to inquire. Thus, a person of ordinary skill in the art would understand that the term "compound" is definite and encompasses a compound that has the characteristics described above.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 112, second paragraph, be withdrawn.

DOCKET NO: ISIS0064-100 (RTS-0175)

PATENT

**II. The Claimed Invention Is Not Obvious**

Claims 1, 2, 4-15<sup>1</sup> are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over the combination of Ishibashi et al., J. Biol. Chem., 1994, 269, 29897-29902 (hereinafter, the "Ishibashi reference"), Sato et al., J. Biochem., 1998, 123, 1119-1126 (hereinafter, the "Sato reference"), Milner et al., Nature Biotechnol., 1997, 15, 537-541 (hereinafter, the "Milner reference"), and U.S. Patent No. 5,801,154 (hereinafter, the "Baracchini reference"). The Office Action asserts that it would have been obvious to target and inhibit expression of DUSP5 *in vitro* by administering oligonucleotides having between 8 and 50 nucleobases targeted to DUSP5 (Office Action at page 3). Applicants respectfully disagree.

In establishing a *prima facie* case of obviousness under 35 U.S.C. §103, it is incumbent upon the Examiner to provide a reason why one of ordinary skill in the art would have been led to modify a prior art reference or to combine reference teachings to arrive at the claimed invention. *Ex parte Clapp*, 227 U.S.P.Q. 972 (Bd. Pat. App. Int. 1985). To this end, the requisite motivation must stem from some teaching, suggestion or inference in the prior art as a whole or from the knowledge generally available to one of ordinary skill in the art and not from appellants' disclosure, see for example, *Uniroyal Inc. v. Rudkin-Wiley Corp.*, 5 U.S.P.Q.2d 1434 (Fed. Cir. 1988); and *Ex parte Nesbit*, 25 U.S.P.Q.2d 1817, 1819 (Bd. Pat. App. Int. 1992). In this respect, the following quotation from *Ex parte Levengood*, 28 U.S.P.Q.2d 1300, 1302 (Pat. Off. Bd. App. 1993), is noteworthy:

Our reviewing courts have often advised the Patent and Trademark Office that it can satisfy the burden of establishing a *prima facie* case of obviousness only by showing some objective teaching in either the prior art, or knowledge generally available to one of ordinary skill in the art, that "would lead" that individual "to combine the relevant teachings of the references." ... Accordingly, an examiner cannot establish obviousness by locating references which describe various aspects of a patent applicant's invention without also providing evidence of the motivating force that would **impel** one skilled in the art to do what the patent applicant has done. (citations omitted; emphasis added)

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<sup>1</sup> Applicants note that claim 11 was previously canceled and is no longer pending.

**DOCKET NO: ISIS0064-100 (RTS-0175)****PATENT**

Significantly, the Office Action identifies no “motivating force” that would “impel” persons of ordinary skill to modify the respective teachings of the cited references and achieve the claimed invention.

The motivation for combining the references in the manner identified in the Office Action is that the Milner reference reports general methods of designing and assessing antisense oligonucleotides for their ability to target and inhibit the expression of a known target gene, and the Ishibashi reference reports the nucleic acid sequence encoding DUSP5 (Office Action at pages 4-5). The Office Action also asserts that the Ishibashi and Sato references report that DUSP5 is involved in a number of cellular events and may be involved in particular pathogenesis. Thus, because DUSP5 is known and general methods of designing and assessing antisense oligonucleotides are known, the Office Action concludes that Applicants’ claimed compounds and methods are obvious. Indeed, taking the Office Action’s reasoning to its logical conclusion, once a protein target is known, then all compounds having 8 to 50 nucleobases targeted to a nucleic acid sequence encoding the protein target that inhibit the expression of the nucleic acid sequence encoding the target, and thus the target, are obvious. This conclusion is not supported by law.

This alleged motivation in no way would lead one skilled in the art to combine the teachings of any references, let alone combine the teachings of the cited references in the manner suggested in the Office Action. Such alleged motivation, at most, raises an inappropriate “obvious to try” standard. Indeed, the court made it clear that it is improper to reject claims as “obvious to try” where the motivation to combine references arises merely because the subject matter of the claimed invention is a promising field for experimentation, although the prior art provides only general guidance as to particular form of the claimed invention or how to achieve it. *In re O’Farrell*, 7 U.S.P.Q.2d 1673, 1681 (Fed. Cir. 1988). Without more specific suggestions in the prior art, there is insufficient motivation to combine the cited references. Furthermore, “focusing on the obviousness of substitutions and differences, instead of the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness.” *Gillette Co. v. S.C. Johnson & Son*, 16 U.S.P.Q.2d 1923, 1927 (Fed. Cir. 1990).

**DOCKET NO: ISIS0064-100 (RTS-0175)****PATENT**

In addition, it appears that the only motivation identified in the Office Action to combine the references is the use of the Applicants' specification and hindsight reconstruction, which is strictly forbidden. *In re Fine*, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988) ("One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."). When assessing whether or not a combination of references would have produced a claimed invention, one must consider the teaching of each reference as a whole without undue emphasis on those features that would support a finding of obviousness. *In re Wesslau*, 147 U.S.P.Q. 391 (C.C.P.A. 1965) (it is impermissible to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what the references fairly suggest to one of ordinary skill in the art).

Consideration of the cited references as a whole for what they each fairly suggest, demonstrates that a person of ordinary skill seeking to combine them would not have produced any claimed invention. In this respect, the Office Action has apparently picked one particular element from the Ishibashi reference, one particular element from the Sato reference, one particular element from the Baracchini reference, and/or one particular element from the Milner reference. One skilled in the art, however, would *not* be motivated to pick and choose only those specific elements referred to in the Office Action from the many elements recited in the references and combine the selected elements in the specific manner indicated in the Office Action. Indeed, it appears that the only guide to picking and choosing particular elements from the cited art of records appears to have been the present application. Thus, the combination of references is improper for, at the very least, failure to provide motivation to combine references and for its use of hindsight reconstruction based upon Applicants' disclosure.

The Federal Circuit has recently affirmed the requirement for motivation to combine references, stating that:

virtually all [inventions] are combinations of old elements. Therefore, an examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed [\*\*10] elements would permit an examiner to use the claimed

## DOCKET NO: ISIS0064-100 (RTS-0175)

## PATENT

invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention . . .

To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and *with no knowledge of the claimed invention*, would select the elements from the cited prior art references for combination in the manner claimed . . .

To counter this potential weakness in the obviousness construct, the suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness.

*Yamanouchi Pharm. Co. v. Danbury Pharm, Inc.*, 231 F.3d 1339 (Fed. Cir. 2000); 56 U.S.P.Q.2d 1641, 1645, citing *In re Rouffet*, 149 F.3d 1350, 1357-58, 47 USPQ2d 1453, 1457-8 (Fed. Cir. 1998) (emphasis supplied). It appears that the Office Action has done what Yamanouchi reaffirms should not be done -- used Applicants' specification as a blueprint.

In addition to establishing an impelling motivation, to set forth a legally sufficient *prima facie* case of obviousness, the Examiner must also show that the cited references teach or suggest a claimed invention with a *reasonable expectation of success*. *In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529, 1531-32 (Fed. Cir. 1988). The Office Action has failed to provide any reasoning that the combining the references in the manner identified therein would have produced Applicants' claimed inventions with a reasonable expectation of success. The Office Action, for example, fails to establish that one skilled in the art combining the teachings of the cited references would produce compounds that inhibit the expression of human DUSP5, let alone inhibit such expression by at least 40%, as recited in claim 1. Indeed, As Table 1 of Applicants' specification shows (see pages 92 to 94 of the specification), many oligonucleotides fail to inhibit the expression of human DUSP5 at all (i.e., show 0% inhibition). Thus, even if one skilled in the art were motivated to combine the cited references in the manner indicated in the Office Action (and Applicants maintain that no such motivation has been established), one skilled in the art would not have had a reasonable expectation of success.

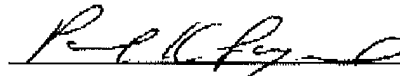
**DOCKET NO: ISIS0064-100 (RTS-0175)****PATENT**

Thus, in view of the foregoing, Applicant respectfully submits that the Office Action has failed to establish a *prima facie* case of obviousness. In particular, the Office Action has failed to provide any motivation that would impel one skilled in the art to modify the cited references so as to produce Applicants' claimed inventions with a reasonable expectation of success. Accordingly, Applicants respectfully request the rejection under 35 U.S.C. §103(a) be withdrawn.

**III. Conclusion**

The claims are in condition for allowance. An early Notice of Allowance is therefore earnestly solicited. Applicant invites the Examiner to contact the undersigned at (215) 665-6914 to clarify any unresolved issues raised by this response.

Respectfully submitted,



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